

Applicants have amended claim 1 to more distinctly claim the subject matter of the invention. Specifically, applicants have amended claim 1 to recite that the interface of part "a)" is the "exposed interface". Claim 1 has been further amended to recite that the modification to the interface results in increased hydrophilicity as compared to the "unmodified form" of the domain or fragment. No new matter has been added by these amendments.

Applicants have amended claim 4 to recite that the amino acids being substituted into the region are more hydrophilic than those "being substituted for". This amendment merely clarifies the language and does not add new matter.

Applicants have canceled, without prejudice, claim 7.

Applicants have amended claims 8-11 to change their dependency from claim 7 (now canceled) to a dependency on claim 1.

Applicants have amended claim 12 to recite the term "exposed interface". This amendment is supported by pending claim 1.

None of these amendments contain new matter.

Claim Objections

Informalities

The Examiner has objected to the Specification,

contending that it is not in the preferred arrangement. Applicants have obviated this rejection with the substitute Specification filed herewith.

The Examiner has objected to the Specification because of the misspelling of the word "superfamily". Applicants have corrected this error in the substitute Specification. Finally, the Examiner contends that there is an unfinished sentence on page 19, line 4. However, "Mutations in the 4-4-20 scFV" is actually a section heading and not a sentence. Therefore, this was not amended in the substitute Specification. Applicants request that the Examiner reconsider and withdraw the outstanding objections in light of these amendments and arguments.

37 C.F.R. § 1.75(c)

The Examiner has objected to 7, contending that it is an improper dependent claim. Applicants have obviated this rejection by canceling claim 7.

Claim Rejections

35 U.S.C. § 112, second paragraph

Claims 1-5, and 7-27 stand rejected under 35 U.S.C. § 112, second paragraph because the Examiner contends that these claims are "indefinite for failing to particularly point out and distinctly claim" the invention. Specifically, the Examiner contends that claim 1 (and claims dependent therefrom) are indefinite because the recitation "an interface" is unclear.

Applicants have obviated this rejection by amending claim 1 to recite "said exposed interface".

Claim 1 stands additionally rejected because the Examiner contends that recitation of the phrase "as compared to" in lines 2-3 of part b is unclear. Applicants have amended claim 1 to recite that the comparison is with respect to the domain or fragment of said parent antibody in "unmodified form". This amendment clarifies the claim.

Claim 2 stands rejected because the Examiner contends that the recitation "interface region" lacks antecedent basis. Applicants have obviated this rejection by amending claim 12 to recite "exposed interface". This term has antecedent basis in claim 1, from which claim 12 now ultimately depends.

Claim 4 and 5 stand rejected as indefinite because the Examiner contends it is not clear what the object of comparison is for the phrase "more hydrophillic". Applicants have amended claim 4 to recite that the amino acids are more hydrophillic "than the one or more amino acids being substituted for". This amendment removes any unclarity noted by the Examiner.

In view of the amended claims, applicants request that the Examiner withdraw the rejections under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 102(b)

The Examiner has maintained her rejection of the claims 1-7, 10, 13-17, and 26-27 under 35 U.S.C. § 102(b) as being

anticipated by Johnson et al. (WO92/01787) ("Johnson").

Specifically, the Examiner reiterates that Johnson teaches "an analogue of a single chain variable domain of a member of an immunoglobulin or immunoglobulin superfamily, in which said analogue one or more interface amino acid residues of the domain is altered" such that the analogue is more hydrophilic than the unaltered domain. In response to applicants' March 5, 2001 Amendment and Reply (which argued that the pending claims were directed towards DNA sequences which encode antibodies comprising modified interfaces, wherein those interfaces exist within a light chain or within a heavy chain of a larger antibody), the Examiner stated that, because applicants' claims encompass scFv, "applicants' claims do encompass an interface between immunoglobulin domains derived from different chains (IE VH from the heavy chain and VL from the light chain)" (emphasis added). Applicants traverse.

Although applicants' claims do encompass modified scFv fragments, claim 1 is clearly limited to DNA sequences comprising modified interfaces which exist "within a light chain or within a heavy chain of a larger antibody fragment or full antibody". Therefore, it is unclear to applicants why the Examiner continues to contend that the claims encompass DNA sequences comprising modified interfaces which exist **between** immunoglobulin domains derived from **different chains** (i.e. between VH from the heavy chain and VL from the light chain). As illustrated in Appendix D, scFv comprises both a VH and a VL. Therefore, a scFv may be

engineered to comprise a modified interface between VL and VH (as recited in Johnson) or, alternatively, may comprise a modified interface **within** a VL or **within** a VH (as recited in the pending claims). Because Johnson defines his "interface" as "the region on a given heavy or light chain of an immunoglobulin which associates with the complementary heavy or light chain" (Johnson, page 13, lines 19-22), no additional exclusitory language is necessary in claim 1 (or claim 10) to distinguish over Johnson. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

35 U.S.C. § 103(a)

The Examiner has maintained her rejection of claims 1-7, 10, 13-17, 18-22, and 26-27 under 35 U.S.C. § 103(a), contending that the claims are unpatentable over Johnson in view of Jenkins et al. (PNAS 92:6057-6061, 1995) ("Jenkins") and Knappik et al. (Biotechniques 17(4): 754-761, 1994) ("Knappik"). Specifically, the Examiner contends that Jenkins and Knappik provide the teaching that Johnson lacks with respect to claims 18-22. Applicants traverse.

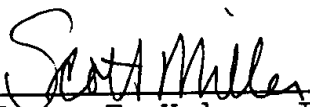
As described above, Johnson does not teach or suggest applicants' instant invention. Further, the combination of Jenkins or Knappik, which the Examiner cites for teaching additional moieties, adds nothing to make up for the lack of teaching in Johnson regarding the underlying DNA sequence itself. For this reason, applicants respectfully request that the

Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).


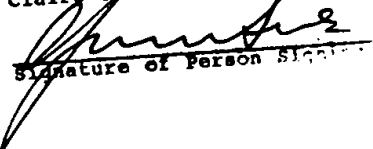
Conclusion

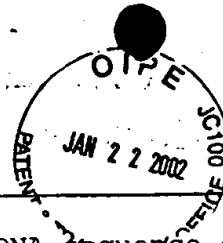
For all of the above reasons, reconsideration and allowance of the pending claims is requested.

Respectfully submitted,


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GI
1. (Four times amended) A DNA sequence capable of encoding a domain or fragment of an antibody, wherein said domain or fragment comprises an exposed interface wherein:

Sub H1
a) said exposed interface allows contact along a longitudinal axis between adjacent domains within a heavy chain or within a light chain of a larger antibody fragment or full antibody;

b) said exposed interface comprises a modification as compared to a domain or fragment of a parent antibody, wherein said modification to said exposed interface results in said domain or fragment of said antibody demonstrating increased hydrophilicity as compared to said domain or fragment of said parent antibody in unmodified form.

2. The DNA sequence according to claim 1 in which said modification is a substitution of one or more amino acids at said region which comprised or would comprise the interface with amino acids which are more hydrophilic.

3. The DNA sequence according to claim 1 in which said modification comprises:

- a) insertion of one or more hydrophilic amino acids;
- b) insertion of one or more amino acids;
- c) deletion of one or more hydrophobic amino acids;

or

- d) deletion of amino acids.

G2
11 Sub 12
4. (Three times amended) The DNA sequence according to claim 1 in which said modification consists of any two or more of:

62
Amended
Sub 52

a) substitution of one or more amino acids at said region which comprised or would comprise the interface with amino acids which are more hydrophilic than the one or more amino acids being substituted for;

b) insertion of one or more hydrophilic amino acids or insertion of amino acids; and

c) deletion of one or more hydrophobic amino acids or deletion of amino acids.

5. The DNA sequence according to any of claims 2 to 4 in which said substituted or inserted amino acid is selected from the group consisting of Asn, Asp, Arg, Gln, Glu, Gly, His, Lys, Ser, and Thr.

63
Sub 13

8. (Amended) The DNA sequence according to claim 1 in which said fragment is a Fab fragment.

9. (Amended) The DNA sequence according to claim 1 in which said fragment is an Fv fragment.

10. (Amended) The DNA sequence according to claim 1 in which said fragment is a scFv fragment.

11. (Amended) The DNA sequence according to claim 1 in which said fragment is an Fv stabilized by an inter-domain disulphide bond.

Sub H3

12. (Amended) The DNA sequence according to any of claims 9 to 11 in which said exposed interface [region] comprises residues 9, 10, 12, 15, 39, 40, 41, 80, 81, 83, 103, 105, 106, 106A, 107, 108 for VL, and residues 9, 10, 11, 13, 14, 41, 42, 43, 84, 87, 89, 105, 108, 110, 112, 113 for VH.

13. The DNA sequence according to claim 1, having a contiguous sequence which encodes one or more additional moieties.

14. The DNA sequence according to claim 13 in which at least one of said additional moieties is a toxin, a cytokine, or a reporter enzyme.

15. The DNA sequence according to claim 13 in which at least one of said additional moieties is at least part of a surface protein of an organism.

16. The DNA sequence according to claim 15 in which said organism is a filamentous bacteriophage.

17. The DNA sequence according to claim 16 in which said surface protein is the geneIII protein.

18. The DNA sequence according to claim 13 in which at least one of said additional moieties is capable of binding a metal ion.

19. The DNA sequence according to claim 18 in which at least one of said additional moieties comprises at least five histidines.

20. The DNA sequence according to claim 13 in which said moiety is a peptide.

21. The DNA sequence according to claim 20 in which said peptide is a labelling tag.

22. The DNA sequence according to claim 21 in which said labelling tag is c-myc or FLAG.

23. The DNA sequence according to claim 20 in which said peptide comprises an association domain which results in self-association of two or more of said antibody fragments.

24. The DNA sequence according to claim 23 in which said association domain is derived from a leucine zipper or from a helix-turn-helix motif.

25. The DNA sequence according to claim 20 in which said peptide comprises a first association domain which results in hetero-association of one or more of said antibody fragments with one or more peptides or proteins comprising a second hetero-association domain being able to associate with said first hetero-association domain.

26. A vector comprising a DNA sequence according to claim 1.

27. A host cell comprising a vector according to claim 26.

1. (Four times amended) A DNA sequence capable of encoding a domain or fragment of an antibody, wherein said domain or fragment comprises an exposed interface wherein:

a) [an] said exposed interface allows contact along a longitudinal axis between adjacent domains within a heavy chain or within a light chain of a larger antibody fragment or full antibody;

b) said exposed interface comprises a modification as compared to a domain or fragment of a parent antibody wherein said modification to said exposed interface results in said domain or fragment of said antibody demonstrating increased hydrophilicity as compared to said domain or fragment of said parent antibody in unmodified form.

4. (Three times amended) The DNA sequence according to claim 1 in which said modification consists of any two or more of:

a) substitution of one or more amino acids at said region which comprised or would comprise the interface with amino acids which are more hydrophilic than the one or more amino acids being substituted for;

b) insertion of one or more hydrophilic amino acids or insertion of amino acids; and

c) deletion of one or more hydrophobic amino acids or deletion of amino acids.

8. (Amended) The DNA sequence according to claim 1 [7] in which said fragment is a Fab fragment.

9. (Amended) The DNA sequence according to claim 1 [7] in which said fragment is an Fv fragment.

10. (Amended) The DNA sequence according to claim 1 [7] in which said fragment is a scFv fragment.

11. (Amended) The DNA sequence according to claim 1 [7] in which said fragment is an Fv stabilized by an inter-domain disulphide bond.

12. (Amended) The DNA sequence according to any of claims 9 to 11 in which said exposed interface [region] comprises residues 9, 10, 12, 15, 39, 40, 41, 80, 81, 83, 103, 105, 106, 106A, 107, 108 for VL, and residues 9, 10, 11, 13, 14, 41, 42, 43, 84, 87, 89, 105, 108, 110, 112, 113 for VH.